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14. ABSTRACT

Metastatic lesions in the proximal femur are a common and serious manifestation of breast cancer. These lesions can be painful and can lead to pathological fracture. Prophylactic surgical fixation is advised in patients thought to be at high risk of fracture and typically involves placement of a prosthetic implant or compression hip screw. This study demonstrated feasibility of an alternative approach, in which proximal femora with metastatic lesions can be repaired by simply filling the defect with bone cement (polymethylmethacrylate), an innovative procedure that could be performed percutaneously and could eliminate the need for implanting hardware in many cases. If defects could be repaired using this technique, patients would benefit from a shorter and less invasive surgical procedure, less pain and discomfort, greatly reduced recovery time, and shorter hospital stays–all at much lower cost. To this end, a mathematical model was developed to evaluate the need for prophylactic surgical fixation for specific patients. This model forms the basis of preliminary guidelines for the proposed surgery. Although viability of the proposed technique was demonstrated for low cyclic loading situations, additional investigation is required to enable further implementation and to ensure fatigue resistance for long-term use.

15. SUBJECT TERMS
Biomechanics; Engineering; Finite Element Analysis; StructuralAnalysis; Bone; Bone Metastases; Pathological Fracture; Hip Fracture; Femur

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Introduction

Metastatic lesions in the proximal femur are a common and serious manifestation of breast cancer. These lesions can be painful and can lead to pathological fracture. Prophylactic surgical fixation is advised in those patients thought to be at high risk of fracture and typically involves placement of a prosthetic implant or a compression hip screw to provide strength. In this study, we investigated whether proximal femora with metastatic lesions can be repaired by simply filling the defect with bone cement (polymethylmethacrylate), an innovative procedure that could be performed percutaneously and could eliminate the need for implanting hardware in many cases. If the metastatic defect could be safely repaired using this new technique, the patient would benefit from a shorter and less invasive surgical procedure, less pain and discomfort, greatly reduced recovery time, and a shorter hospital stay—all at much lower cost. Using finite element (FE) analysis, this study developed a mathematical model which could eventually be used clinically to identify patients with proximal femoral metastases who need surgical intervention. Viability of the proposed percutaneous surgical procedure was also demonstrated for, at a minimum, low cyclic loading situations. This data, when combined with further extensive analysis of fatigue resistance of the cement construct, will enable rapid and safe clinical implementation of the new repair technique and surgical guidelines.

Body

During Year 1 of this study, feasibility of the repair technique was evaluated with mechanical testing of twelve matched pairs of cadaveric proximal femora [Task 1a]. A roughly spherical defect, simulating a metastatic lesion, was introduced and subsequently repaired using the proposed technique in one randomly selected proximal femur from each pair [Task 1b, 1c].

All 24 femora were CT scanned for a separate phase of the study before mechanical testing to failure [Task 1d]. To assess the feasibility of the surgical procedure, *measured %intact* was calculated for each matched pair of specimens as the measured fracture load for the repaired femur divided by the measured fracture load for the contralateral intact femur [Task 1g]. The mean and standard deviation (SD) of *measured %intact* were 94.7% and 8.7%, respectively, indicating with 95% confidence that 95% of the population would have a *measured %intact* greater than 70%, and 50% of the population would have a *measured %intact* greater than 90% [Task 1h]. These strong results clearly support the feasibility of the percutaneous repair technique [Task 1i] and have been presented in numerous abstracts [Kaneko et al., 2005; Keyak et al., 2005a-c] and a conditionally accepted article in Medical Engineering and Physics.

In order to enable further evaluation of the proposed technique, as well as the development of clinical guidelines for its use, the finite element (FE) modeling technique pioneered by Dr. Keyak was further refined and validated for use with proximal femora containing bone cement. To improve the accuracy of the FE modeling method, which previously systematically overestimated the measured fracture load of proximal femora (Keyak, 2001), the relationships used to calculate mechanical properties for the FE models from the CT scan data were modified [Task 1f, 1h, 1j]. These relationships were adjusted until the resulting relationship between the measured and predicted fracture loads of a calibration set of femora (different from the femora obtained for this study) was approximately 1:1, with slope and intercept not significantly different from one and zero, respectively [Task 1k]. After this calibration step was complete, FE models were created from the CT scan data of the twelve intact femora obtained previously and compared with the mechanical testing data, thereby serving as an independent data set on which to validate the calibrated modeling method. These results were presented to the

Orthopaedic Research Society [Kaneko and Keyak, 2004] and in Clinical Orthopaedics and Related Research [Keyak et al., 2005e].

Finite element models were also created from the CT scan data of the repaired femora [Task 1f] to validate the use of the FE modeling method for predicting the strength of proximal femora containing bone cement, with mechanical properties for bone cement obtained from the extensive available literature [Task 1e] (Saha and Pal, 1984). Analysis of covariance was used to compare regression equations between the measured fracture load and the FE-predicted fracture load for the intact and the repaired femora [Task 1h]. These equations were both significant and not significantly different from each other, indicating that the presence of bone cement in the repaired femora did not affect the validity of the FE models, and that the strength predictions for the intact and repaired femora could be compared [Task 1j]. These results were presented to the Orthopaedic Research Society [Keyak et al., 2006] and are currently in preparation for journal submission.

The validity of the FE models for predicting the strength of proximal femora both with and without bone cement also allowed for their use in further evaluating the effect of metastatic lesions and their subsequent repair using the proposed technique. For this purpose, computer programs were developed during Year 2 [Task 2a] and used to create FE models of proximal femora with simulated metastatic defects, allowing the effect of various defect sizes and locations to be studied. (As described in the Year 3 Annual Report, the methods outlined in Tasks 2b and 2c were modified to provide a more expansive analysis.) The computer programs also allowed the modeling of the drill hole that would be created when repairing these defects using the proposed percutaneous repair technique. When the FE models were used to simulate repair, the defect and drill hole were assigned the mechanical properties of bone cement (Saha and Pal, 1984). Since the computer programs allowed defects to be simulated in the CT scan data of the intact femora, the FE-predicted fracture load of each femur in its altered state was directly compared to (divided by) the FE-predicted fracture load of the femur in its intact state. These measures were called *pre-repair %intact* and *post-repair %intact* for defect models before and after simulated repair, respectively.

To model the effect of metastatic lesions in the femoral neck, 423 FE models were created with defects of varying sizes and locations. Defects were created with diameters of 10, 15 and 20 mm, and were located in the inferomedial (IM), superolateral (SL), anterior (A), and posterior (P) aspects of the neck, as well as in the middle of the neck where there was no involvement of the cortex. Additionally, to measure the effect of slight changes in defect locations, defects in the IM, SL, A and P aspects of the neck were moved 1-2 mm away from the cortex, in either direction, at each location. The data from these FE models indicated two important findings. Defects in the IM aspect of the neck were of greatest importance, with large decreases in *pre-repair %intact* (mean 49.9% for 20-mm diameter defects), an effect presumed due to the high stress in this region during stance-type loading conditions. Conversely, 20-mm diameter defects in the other aspects of the neck resulted in a mean *pre-repair %intact* of 91.8%. Additionally, for these loading conditions, the preliminary findings indicated that there was not a critical defect size beyond which the repair technique could not be used, i.e. *post-repair %intact* for the repaired models always approached 100%.

During the past one year no-cost extension, the computer programs written in Task 2a were used, along with the finite element modeling technique validated in Task 1j, to further analyze the structural effect of defects of differing sizes and locations, as well as the effect of the percutaneous repair of these defects. Specifically, defects were modeled in the subcapital region superior to the femoral neck (Head, 27 models) and at and around the level of the lesser trochanter (LT, 606 models), two common and structurally important locations of metastatic lesions.

For the Head defects, defect diameters of 10, 15, and 20 mm were analyzed and resulted in pre-repair strength decreases that were comparable in magnitude to defects in the IM aspect of the neck (mean *pre-repair %intact* for 20-mm diameter defects, 58.4%). Additionally, the repair technique was simulated for all Head defects with *pre-repair %intact* less than 70%, resulting in an average *post-repair %intact* of 127%, and indicating the viability of the proposed technique for repairing defects at this location. This data has been combined with the data from defects in the femoral neck in the development of a mathematical model ($p < 0.001$, R = 0.898) that can be used clinically to evaluate the need for the proposed surgical technique for specific patients [Tasks 2d, 2e]. This model predicts *pre-repair %intact* for a patient with metastases in the femoral neck, given easily measurable anatomic (size of the femoral neck, thickness of the inferomedial cortex) and tumor (tumor size, location) parameters. These results are currently being prepared for journal submission.

For the LT defects, defect diameters of 15 and 20 mm were analyzed for all bones, with additional 25-mm diameter defects analyzed for larger bones. For each defect diameter, FE models were created and analyzed for defects in nine locations at the level of the lesser trochanter. These locations originated from the anterior-medial corner of the bone, with additional defects moved 1.5 and 3 mm posterior and/or lateral from this location (Fig. 1). Additionally, 20 mm diameter defects were used to assess the effect of longitudinal position around the level of the lesser trochanter by varying the placement of the defects in the superior-inferior direction by 4 and 7 mm. Defects in the anterior-medial corner of the bone resulted in the largest decrease in bone strength, averaging 63% of the intact strength for 20 mm diameter defects (Fig. 1, upper left corner). Defects that were lateral and/or posterior to this location had a lesser effect (Fig. 1). However, defects along the medial cortex were slightly more destructive than defects along the anterior cortex. These trends will be useful for predicting *pre-repair %intact* when defects are at the level of the lesser trochanter. Additionally, the repair technique was simulated for all LT defects with *pre-repair %intact* less than 70%, resulting in an average *post-repair %intact* of 99% (97% to 101%). Therefore, this surgery would also be appropriate for tumors at the level of the lesser trochanter. These results are currently being prepared for journal submission.

The above and previously reported findings apply only to static loading. We have also investigated the fatigue strength of the surgical construct by examining the maximum von Mises stress in the cement of each repaired FE model for conditions comparable to that during walking (~3 times BW applied to the femoral head). By comparing this stress (typically 10-20 MPa) with the compressive fatigue strength (endurance limit) of Simplex® P bone cement (50 MPa) (www.orthovita.com/products/cortoss/ous/fatigue.html), the risk of fatigue failure was evaluated for each repaired FE model. Use of von Mises stress accounted for the multiaxial stress field in the cement (Shigley and Mischke, 1989). This approach included a number of assumptions, most of which cannot be readily tested. Although the von Mises stresses presented here represent a significant factor of safety when compared to the compressive endurance limit, the bone cement is not in a purely compressive stress state. Therefore, these stresses, when compared to the tensile endurance limit (9.3 MPa) (www.orthovita.com/products/cortoss/ous/fatigue.html), may actually result in fatigue failure of the cement construct. The actual stress state of the cement during repetitive loading is difficult to predict and will require additional testing and analysis to ensure viability for long-term loading applications. Additionally, it may be possible to increase the fatigue resistance of the cement construct by the addition of reinforcements (Kotha et al., 2004 and references therein) or by lining the drill hole with a carbon fiber sleeve (de Bakker et al., 2006). However, the static results presented here indicate that the percutaneous technique can safely be used for short term or low cyclic loading situations (i.e. for patients who are bedridden, who are wheel-chair bound, or who have short life expectancies).

Key Research Accomplishments

- 27 FE models were created and analyzed to measure the structural effects of simulated metastatic defects in the subcapital region superior to the femoral neck (Head defects).
- This data was combined with data for defects in the femoral neck and used to develop a mathematical model ($p < 0.001$, R = 0.898) to predict *pre-repair %intact* for a patient with simulated defects in the femoral neck, given measured anatomic and tumor parameters.
- The simulated repair of these Head defects resulted in a mean *post-repair %intact* of 127%.
- 606 FE models were created and analyzed to measure the effects of simulated metastatic defects at various locations at or near the level of the lesser trochanter (LT defects).
- The simulated repair of these LT defects resulted in a mean *post-repair %intact* of 99%.
- The maximum von Mises stress in cement elements for loading conditions similar to those during walking are well below the compressive endurance limit for bone cement, but at or above the tensile endurance limit. Further analysis is required.

Reportable Outcomes

Keyak JH, Kaneko TS, Skinner HB: Feasibility of a percutaneous technique for repairing proximal femora with metastatic lesions. Era of Hope, Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, 6/8-11/05. [abstract and poster presentation]

Kaneko TS, Skinner HB, Keyak JH: Feasibility of a percutaneous technique for repairing proximal femora with metastatic lesions. UC System-wide Bioengineering Symposium, Santa Cruz, CA, 6/25-27/05. [abstract, podium and poster presentation, Symposium Poster Award of Excellence]

Keyak JH, Kaneko TS, Skinner HB: Feasibility of a percutaneous technique for repairing proximal femora with metastatic lesions. College of Medicine Faculty Research Poster Session, University of California, Irvine, CA, 10/26/05. [poster presentation]

Keyak JH, Kaneko TS, Rossi SA, Pejcic MR, Tehranzadeh J, Skinner HB: Predicting the strength of femoral shafts with and without metastatic lesions. Clin Orthop Rel Res 439:161-70, 2005.

Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB: Predicting proximal femoral strength using structural engineering models. Clin Orthop Rel Res 437:219-28, 2005.

Keyak JH, Kaneko TS, Skinner HB: Finite element model evaluation of a percutaneous technique for repairing proximal femora with metastatic lesions. Orthopaedic Research Society, 52nd Annual Meeting, Chicago, IL, 3/19-22/06. [abstract and poster presentation]

Kaneko TS, Skinner HB, Keyak JH: Feasibility of a percutaneous technique for repairing proximal femora with simulated metastatic lesions. Med Eng Phys (conditionally accepted).

Grant Proposal: Minimally Invasive Repair of Proximal Femora with Metastatic Lesions. PI: Keyak JH. National Institutes of Health R21. Applied: August 9, 2004.

Grant Proposal: Orthopaedic Evaluation and Treatment of Proximal Femora with Metastases. PI: Keyak JH. National Institutes of Health R01. Applied: October 1, 2005.

Tadashi S. Kaneko, Master of Science, Biomedical Engineering, University of California, Irvine. Conferred: April, 2006.

Conclusions

Conventional surgery to prevent pathological fracture, involving implantation of hardware, is invasive. If a metastatic defect can be safely repaired percutaneously by simply filling the defect with bone cement, the patient would benefit from a shorter and less invasive surgical procedure with less pain and discomfort, greatly reduced recovery time, and shorter hospital stay – all at much lower cost.

The decision to perform prophylactic fixation is complicated by the inadequacy of tools for identifying patients in need of fixation [Hipp et al., 1995]. We addressed this issue by developing a mathematical model to predict the decrease in proximal femoral strength due to a lesion of specified size and location, thus providing preliminary clinical guidelines for identifying those patients requiring surgical intervention. More significantly, this study established efficacy of a minimally-invasive alternative to traditional surgical fixation that will reduce the reluctance to perform surgical repair in those cases where the need for intervention is unclear.

The results of this study indicate that the proposed minimally invasive procedure is a viable option for, at a minimum, situations with low cyclic loading, such as for patients who are bedridden, who are wheel chair bound, or who have short life expectancies. Viability of the procedure is unclear for high cyclic loading conditions in which the cement construct may be at risk of fatigue, an issue which will require further investigation and analysis.

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Keyak JH, Kaneko TS, Rossi SA, Pejcic MR, Tehranzadeh J, Skinner HB. Predicting the strength of femoral shafts with and without metastatic lesions. Clin Orthop Rel Res 439:161-70, 2005d.

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Kaneko TS, Skinner HB, Keyak JH. Feasibility of a percutaneous technique for repairing proximal femora with simulated metastatic lesions. Med Eng Phys (conditionally accepted).

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Supporting Data

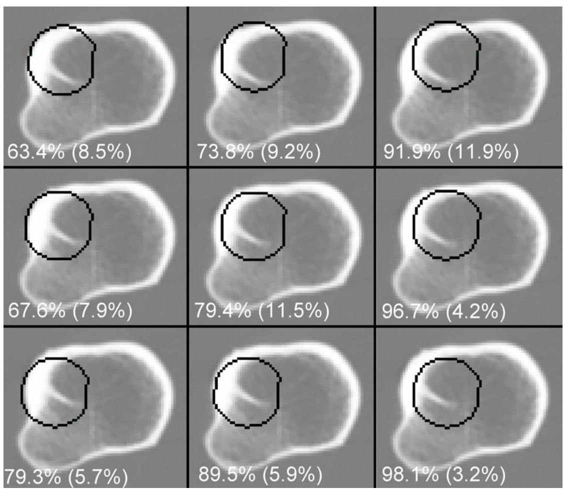

Fig. 1. The nine defect locations at the level of the lesser trochanter are shown for a representative femur. The defect is represented by a circle within a CT scan slice. Top left, the defect in the anterior-medial corner. Each additional picture shows the defect moved laterally (right) and/or posteriorly (down), in increments of 1.5 mm. The mean and standard deviation of *pre-repair %intact* for all 12 bones is shown.